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Heart-Lung Interactions in Aerospace Medicine

HAROLD J. B. GUY and GORDON KIM PRISK

University of California, San Diego
La Jolla, California

Plus ça change, plus c'est la meme chose.
Alphonse Karr, 1849

I. Introduction

Few of the heart-lung interactions that are discussed in this volume have been studied in any detail in the aerospace environment, but it seems to us that many such interactions must occur in the setting of altered accelerative loadings and pressure breathing. That few investigations are in progress suggests that clinical and academic laboratory investigators and aerospace organizations are further apart than during the pioneering work on pressure breathing and acceleration tolerance in the 1940s.

Our purpose is to reintroduce some of the perennial problems of aviation physiology as well as some newer aerospace concerns that may be of interest. We speculate about many possible heart-lung interactions, by necessity often drawing on data from within the aviation field, collected before the modern understanding of these interactions developed, or on recent laboratory data that may not be strictly applicable. In the field of zero-gravity effects, speculation inevitably outruns the sparse available data.

In this chapter, we assume less familiarity with the aerospace environment than with heart-lung interactions.

II. Acceleration and Gravitation

The force exerted by the gravity of the Earth on a mass, m, is given by

$$W = m \cdot g$$

where W is the weight of the mass on the Earth's surface and g is the acceleration due to the Earth's gravity (9.81 $m \cdot sec^{-2}$). Similar "inertial" forces are generated by acceleration (a), where

$$F = m \cdot a$$

The inertial and gravitational force vectors can be summed to give the total accelerative loading. In aviation, these loadings can be large, and it is convenient to compare these with the normal gravitational loading. This is done by normalizing a resultant acceleration (a) with reference to the standard gravitational acceleration g, leading to the 'G' system in which

$$G = a/g$$

In aviation, aerodynamic forces and thrust produce the accelerations. If the resultant of these forces (F) is twice the weight of a body, the accelerative loading is 2G, and generally:

$$G = F/W = ma/mg$$

where W is the weight of the vehicle. An aircraft flying level at constant velocity, generates a net resultant aerodynamic force (here simply lift) equal to its own weight, and G is, therefore, 1. When speed is adequate, the lift force can be increased very readily by increasing the angle of attack of the wing (pulling on the yoke). This increases the lift/weight ratio (F/W), and thus G.

The mechanics of flight are such that an increase in lift (which is at right angles to the velocity vector, v), will cause a radial (centripetal) acceleration of magnitude

$$a = v^2/r$$

Because the radius (r) of any turn or loop is large, the radial acceleration is physiologically equivalent to linear acceleration. Aircraft crew are so oriented that the acceleration vector resulting from lift is in the foot-to-head direction. This leads to a downward (head-to-foot) gravitoinertial G force that is termed $+G_z$, according to the following convention:

G force direction	Terminology
Backward (front-to-back)	$+G_x$
Forward (back-to-front)	$-G_x$
Transverse < to the left	$+G_y$
Transverse > to the right	$-G_y$
Downward (head-to-foot)	$+G_z$
Upward (foot-to-head)	$-G_z$

These forces can be colorfully described as; "eyeballs in" for $+G_x$, "eyeballs left" for $+G_y$, "eyeballs down" for $+G_z$, and so on.

III. Increased Foot-to-Head Acceleration ($+G_z$)

In 1919, a pilot reported alarming incapacitation while attempting to discover the smallest turning circle of a Sopwith triplane. He noted a "graying of the sky," fainted, and woke up flying over a village a mile away from the site of his experiment (Clark et al., 1961). He was exposed to $+4.5G_z$. The incapacitation he described is still a major cause of flying incidents and fatal accidents (Burton and Whinnery, 1985).

Large centrifuges were developed in the 1930s to explore human acceleration tolerance. A centrifuge rotating at 22 rpm will provide 5G radial acceleration in a gondola 30 ft from the axis. This radial component, and the normal 1G gravitational component result in $+5.1G$ at that point.

A. Normal Human Tolerance of $+G_z$

Impairment of vision ranging from "grayout" (peripheral vision loss) to total "blackout" limit the aviator's tolerance of $+G_z$, and are generally used as the physiological endpoints in acceleration research. Useful plots of G tolerance as a function of time were developed using these endpoints (Fig. 1). There is, however, marked intra- and intersubject variation in $+G_z$ tolerance. Neither centrifuge data nor the onset of visual symptoms can provide safe operational limits. Unconsciousness can occur at below $+4G_z$, and it is likely to occur without warning at high $+G_z$ onset rates (Burton and Whinnery, 1985). Although circulatory disturbances obviously limit $+G_z$ tolerance, we will see that they should be considered in the context of other thoracic effects.

B. Lung Function During Increased $+G_z$

The sensitivity of the pulmonary circulation to $+G_z$ has been recognized for many years (Gauer and Bondurant, 1961), but until recently, there has been less awareness of the marked effects of $+G_z$ on regional lung volumes, ventilation, and pleural pressure. Interest in the effects of $+G_z$ on the lung was increased when respiratory symptoms were described in pilots who breathed oxygen while exposed to $+G_z$ (Langdon and Reynolds, 1961).

Distribution of Ventilation

Morphometric studies in dogs showed that the gradient in alveolar size that is present at $+1G_z$ is further increased on exposure to $+G_z$ (Glazier and Hughes, 1968). The gradient is highlighted if an abdominal binder is used to prevent excessive descent of the diaphragm. In humans, the normal

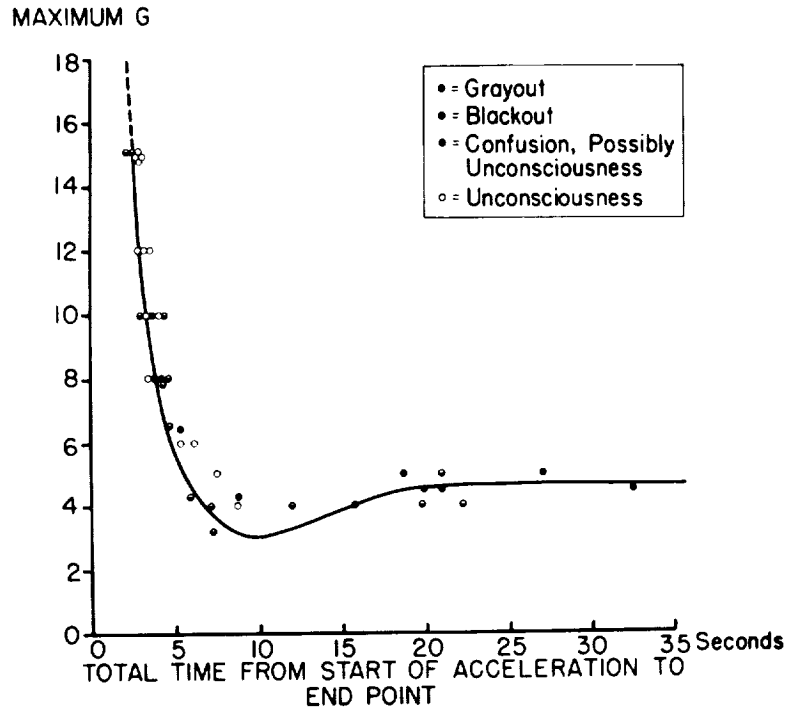


Figure 1 Normal human tolerance to $+G_z$. Data collected from a number of sources by Stoll (1956). Notice the correspondence between the dip in tolerance and the minimum systemic arterial pressure seen in Figure 2 (published with permission).

topographic gradient in ventilation seen at $+1G_z$ is accentuated as G_z increases. Airways closure also increases, especially when descent of the diaphragm is prevented by an inflated abdominal G-suit bladder and can occur during tidal breathing as the expiratory reserve volume is reduced (Glaister, 1970, 1977).

Distribution of Perfusion

Regional pulmonary blood flow in the lung is critically dependent on the local pulmonary arterial and venous pressures (P_a, P_v). which are subject to gravitational gradients, and on alveolar pressure (P_A), which is not (except possibly beyond closed airways). These gradients lead to three distinct zones in the lung at $+1G_z$ (West et al., 1964).

Zone 1 ($P_A > P_a > P_v$), in which perfusion is absent, is normally restricted to the lung apices.

Zone 2 ($P_a > P_A > P_v$), in which perfusion depends upon the arterial-alveolar pressure difference and, thus, changes steeply down the lung.

Zone 3 ($P_a > P_v > P_A$), in which perfusion depends on the arterial-venous pressure difference, which is large and constant.

The topographic distribution of these zones should depend upon the value and orientation of G, and should be readily predictable from the current P_a, P_v, and P_A values. Glaister (1970) measured P_a at $+1$ to $+2.8G_z$ in human subjects. He found that P_a was linearly related to $+G_z$, as it must be in a hydrostatic system in which the pressure is remaining constant at one point (the "hydrostatic indifference" point). The calculated hydrostatic indifference (constant pressure) point here was 5 cm below the pulmonary trunk. He assumed that transvascular pressure across the pulmonary veins in the hilum would not fall below zero and, thereby, estimated the topographic distribution of venous pressure. Zone 1 was estimated to occupy the upper half of the lung at $+3G_z$.

Permutt (1967) pointed out that the greatest changes in zone 1 should occur just above the $+G_z$ value where it first appears because the height (h) perfused above the point of hydrostatic indifference, at a constant pressure head (P) is inversely related to $+G_z$:

$$h = P/(\rho \cdot g \cdot G_z)$$

where ρ is the specific gravity of blood.

Zone 2 can be predicted to be short: $P_a > P_A > P_v$ is true from the point at which $P_A = P_a$ to the point where $P_A = P_v$. The difference in height (h) between these points is:

$$h = (P_a - P_v)/(\rho \cdot g \cdot G_z).$$

It can be seen that zone 2 height should be only 3.3 cm at $+3G_z$ (versus 10 cm at $+1G_z$) if $P_a - P_v$ is 7.6 torr. As a consequence, most of the lung should be either in the zone 1 or zone 3 state, during increased $+G_z$.

Bryan et al. (1965) performed ^{131}I-labeled macroaggregated albumin perfusion scans during $+1$ to $+4G_z$ accelerations. That study, along with later ^{133}Xe studies, confirmed the theoretical predictions in general, although zone 2 could not be clearly distinguished from zone 3, and there seemed to be a steady increase in perfusion down the lower lung regions. This may be so because compression of dependent alveoli would increase flow per unit lung volume (the measured quantity) at a constant flow per capillary unit (Glaister, 1977).

Distribution of Gas Exchange

There is a steady fall in the Pa_{O_2} of dogs exposed to $+G_z$ while breathing air, especially if the otherwise marked descent of the diaphragm is prevented by abdominal binding (Glaister, 1968) or inflation of the abdominal bladder of a G-suit (Modell et al., 1985). Aviators strain, and abdominal bladders of G-suits inflate during $+G_z$, and both these actions limit diaphragm descent. Aviators become hypoxemic during $+G_z$ while breathing air (Barr, 1962). Although this hypoxemia could be simply consistent with the increased topographic inhomogeneity of both ventilation and perfusion, dependent airways closure is prominent, and the major cause of the hypoxemia is almost certainly the attendant population of extremely low ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}_c$) units (Glaister, 1970).

The Oxygen Atelectasis Problem

The rate of absorption of gas from low $\dot{V}_A/\dot{Q}_c$ units and the critical $\dot{V}_A/\dot{Q}_c$ leading to atelectasis, both rise as the F_{IO_2} rises (Dantzker et al., 1975). Thus, the combination of a raised F_{IO_2}, a G-suit, and $+G_z$, predictably leads to basal atelectasis. Lower F_{IO_2} mixtures, and pressure breathing can be used to minimize this problem (Glaister, 1970; Shubrooks, 1973).

Pleural Pressure Gradients

Modell and Baumgardner (1984) found that apical (craniad) pleural pressures became increasingly negative with increasing $+G_z$ (craniocaudal **G** vector) in pigs and dogs. The basal (caudad) pleural pressures were near atmospheric during relaxation, but they became extremely high (+ 20 cmH_2O at $+5G_z$) with abdominal G-suit inflation. It seems that the lung can be virtually suspended by strongly negative apical pressures in the relaxed state, or it can be supported by massively positive diaphragmatic pleural (and abdominal) pressures with G-suit inflation. This implies that the pericardial pressure must also be markedly influenced by abdominal tone and G-suit status.

C. Cardiovascular Effects of $+G_z$

The principal hemodynamic effect of arising from the lying posture is a redistribution of venous volume, with approximately 500 ml of blood pooling in the legs (Blomqvist and Stone, 1985). However, the hemodynamic effects of increasing $+G_z$ are somewhat different, and direct arterial hydrostatic effects are of greater importance.

Direct Hydrostatic Effects

In 1946, Lambert and Wood showed that eye-level arterial pressure falls by about 32 torr/G_z. This corresponds with a hydrostatic indifference point

at heart level. They noted no visual disturbances with eye-level pressures above 50 torr. Systolic pressures of 20 torr (approximately the intraocular pressure) were associated with complete loss of vision.

Venous Return

Increasing $+G_z$ causes 12–50 ml/G_z blood pooling in the legs. This initial blood pooling, which takes 25 sec, is followed by a slow increase in leg volume, with about 70 ml/G_z accumulation in 5 min (Glaister, 1970). This is a modest volume when compared with the 500 ml that pools in the legs during the transition from lying to standing, and it probably reflects the difference between the filling of collapsed veins and the distention of them, with venoconstriction counteracting the latter process.

Many workers assume that splanchnic pooling occurs, but in humans transmural pressures in the abdomen do not increase. Rushmer (1947) found intra-abdominal pressure rose by 15 torr/G_z, providing an approximate balance to the intravascular hydrostatic gradient. The situation may, however, be different in anesthetized animals with more relaxed abdominal muscles.

The blood redistribution resulting from increasing G_z might be expected to decrease the cardiac preload and the atrial and ventricular end-diastolic pressures. Before reviewing such data, it is important to stress that hydrostatic gradients cause major measurement errors at $+G_z$. Subjects, and the seats or harnesses used, sag under stress and, thus, the hydrostatic relationship of any catheter tip to a fixed transducer changes. This leads to a large apparent change in pressure (e.g., 3.9 torr/cm at $+5G_z$).

Glaister (1970), while studying a single subject, recorded a fall of right atrial pressure (referred to pulmonary trunk level) from zero to − 7 torr at $+3G_z$. Peterson et al. (1977) measured left ventricular end-diastolic pressure (LVEDP) in lightly anesthetized, chronically instrumented dogs. At $+3G_z$, when aortic flow had fallen to 33% of the control value the LVEDP had fallen from + 1.4 torr to − 5 torr. Dye-dilution studies report an 18 to 24% decrease in cardiac output shortly after the onset of $+3G_z$ (Lindberg et al., 1960; Rosenhamer, 1967). Boutellier and coworkers (1985), obtained similar results using a CO_2-rebreathing technique.

Reduction in cardiac output during exposure to $+G_z$ may be entirely due to simple loss of venous return and preload reduction. However, this explanation is as tentative as were similar early explanations of the effects of positive end-expiratory pressure (PEEP).

Possible Mechanical Heart-Lung Interactions

Peterson and associates (1977) found that although G-suit inflation could maintain LVEDP at higher than normal values during $+6G_z$ in their

permanently instrumented dogs, cardiac output remained well below the control value. This is a most interesting observation.

Total peripheral resistance was greatly elevated (217% of control—largely because of the occlusive effect of the G-suit), and this increase in afterload must have contributed to the low cardiac output. The authors did, however, speculate that high abdominal pressures generated by the G-suit may have increased pericardial pressure. When one considers the later measurements of basal pleural pressure made by Modell and Baumgardner (1984) with values of + 20 cmH_2O in G-suited dogs at $+5G_z$, these speculations seem increasingly relevant.

It now seems important to make direct transcardiac pressure measurements, or carefully follow chamber volumes, when studying cardiac performance at the limits of $+G_z$ tolerance. Direct mechanical heart-lung interactions are likely, and it is possible that basal lung compression and airways closure may effectively embed the heart in a noncompliant tissue.

Reflex Effects

After an initial fall upon exposure to $+G_z$, head-level arterial pressure climbs back toward normal, and there is an associated tachycardia. After return to $+1G_z$, there is a brief arterial pressure overshoot. Similar changes are seen in the dog femoral arterial tracing in Figure 2 (Glaister, 1970), and the response can be seen to differ from that seen in the passive pulmonary circulatory system.

Carotid baroreceptor activity is probably largely responsible for the secondary rise (Peterson and Bishop, 1979; Abboud et al., 1979). Both cardioacceleration and active arteriolar vasoconstriction occur. Although splanchnic vasoconstriction is related to falling carotid pressure, probably the decreased activity of the low-pressure central mechanoreceptors causes vasoconstriction in limb muscle beds (Donald and Shepherd, 1978; Blomqvist and Stone, 1985).

Venous return is also augmented. Salzman and Leverett (1956) demonstrated dog saphenous vein constriction during $+G_z$, and Hiatt et al. (1958) showed similar constriction in human forearm and saphenous veins. Venomotor activity is potentiated by high distending pressures (Öberg, 1967; Blomqvist and Stone, 1985). Whereas splanchnic veins probably constrict in response to arterial baroreceptor stimulation, cutaneous veins have been shown to constrict in response to active respiratory effort (Browse and Hardwick, 1969), such as occurs in both humans and pigs, in response to $+G_z$ (discussed later).

D. Protective Measures

Straining Maneuvers

Early investigators soon learned that $+G_z$ tolerance could be voluntarily extended. Lambert and Wood (1946) wrote:

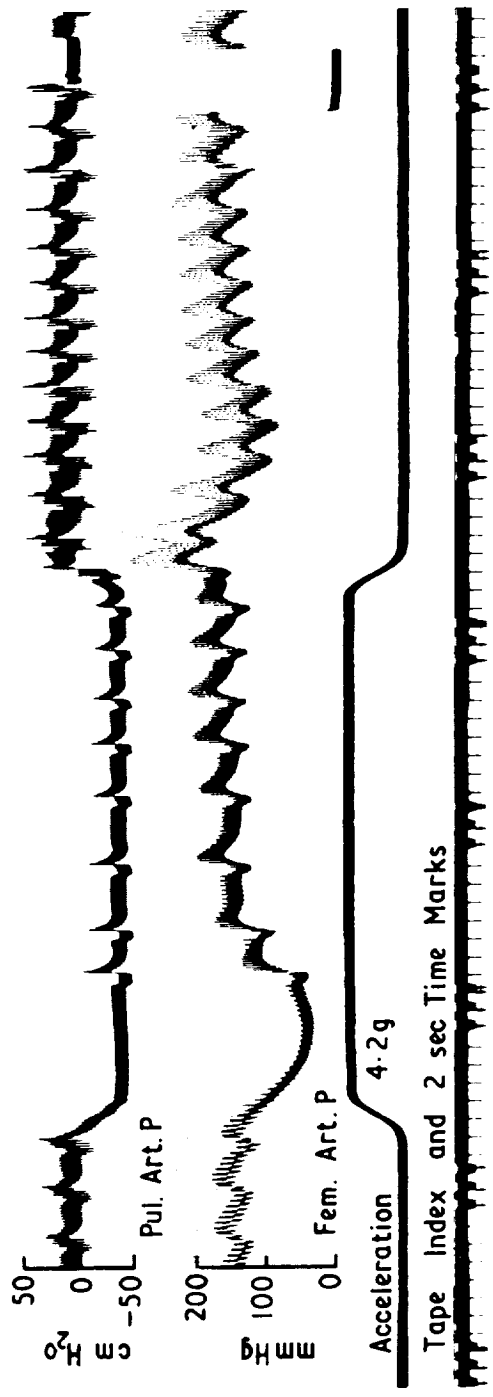


Figure 2 Records of pulmonary arterial pressure referenced to the level of the pulmonary trunk, and femoral arterial pressure referenced to the level of the left ventricle from an anesthetized dog exposed to $+4.2G_z$ for 1 min (from Glaister, 1968, with permission).

> Some of the straining procedures used by veteran pilots have been selected and refined on the basis of centrifuge studies to produce a very effective maneuver. This consists essentially of a series of rapidly repeated forced expirations against a partially closed glottis coordinated with muscular straining.

This maneuver was called the "M-1 anti-G straining maneuver." It now also involves crouching down in the seat as much as possible, and the glottis can be completely closed (Shubrooks and Leverett, 1973). Cohen (1983) found that the M-1 maneuver improved tolerance limts from a mean of $+3.2G_z$ in the relaxed state, to $+4.9G_z$. It is perhaps puzzling that performing a Valsalva-like maneuver, which has been used to decrease tolerance of $+1G_z$ (Howard et al., 1951), can improve $+G_z$ tolerance. The M-1 maneuver, however, includes some actions that are not generally performed when the Valsalva maneuver is performed in other settings.

The tensing of muscles is an important part of the M-1 maneuver and has major cardiovascular effects. Lohrbauer et al. (1972) demonstrated that protection rivaling that of the full M-1 maneuver (peripheral light loss at $+4.5G_z$ vs. $+3.6G_z$ relaxed) was afforded by sustaining a handgrip at 30–50% maximum while maintaining baseline intrathoracic and intragastric pressures. The handgrip produced a 25-torr mean arterial pressure elevation, associated with significant tachycardia, during control runs at $+1G_z$. In lightly anesthetized cats, muscle contraction increases blood pressure, heart rate, and contractility by reflexes mediated by group III and IV muscle afferents (Kaufman et al., 1984). Exercise evokes venoconstriction in humans probably by similar reflexes (Fortney et al., 1983).

It is instructive to compare the thoracic part of the M-1 maneuver with the normal Valsalva maneuver (Fig. 3). Eckberg (1980) has reviewed the latter maneuver in more detail.

Phase I

The initial rise in blood pressure has two potential sources. First, direct transmission of increased intrathoracic pressure to the arterial system; and second, an increased stroke volume resulting from the ventricular unloading effects of increased intrathoracic pressure. Note that phase I is associated with a slowing of the heart rate, as a result of carotid baroreceptor stimulation in the normal $+1G_z$ environment, and that this must reduce the rise in blood pressure.

At $+G$ this parasympathetic effect will be much less because carotid level blood pressure is much lowered by a direct hydrostatic effect. Burns et al. (1986) studied G-suit-equipped conscious miniature swine, exposed to $+G_z$. Grunting momentarily raised esophageal pressure up to 60 torr

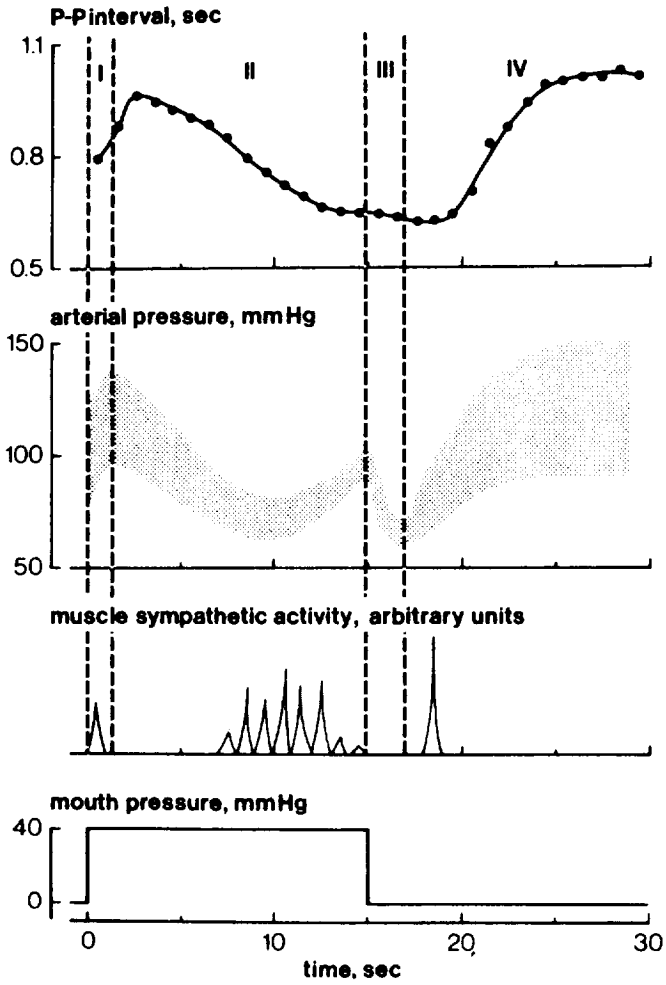


Figure 3 Schematic representation of a normal response to the Valsalva maneuver. The four phases detailed in the text are indicated by Roman numerals (from Eckberg, 1980, with permission).

and eye-level arterial pressure almost the same amount (Fig. 4). Thus, aortic transmural pressure remained approximately constant.

Phase II

The secondary fall in blood pressure is due to a decreased venous return and, thus, shortly after, a decrease in cardiac output.

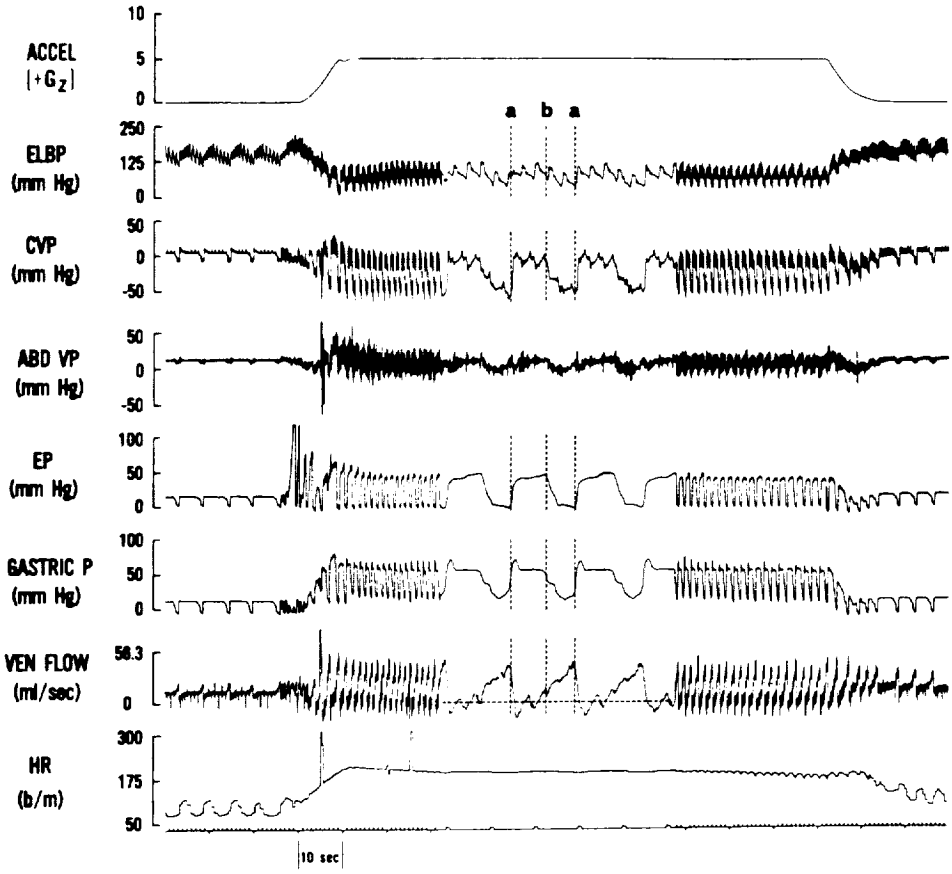


Figure 4 Influence of repetitive anti-G straining as evidenced by esophageal pressure (EP) changes in a G-suited miniature swine exposed to $+G_z$ as indicated. The other measurements are: ELBP, eye-level blood pressure; CVP, central venous pressure recorded in the superior vena cava; ABD VP, abdominal venous pressure recorded in the abdominal vena cava; GASTRIC P, gastric pressure recorded in the stomach; VEN FLOW, venous blood flow in the inferior vena cava recorded at the diaphragm; HR, heart rate. Note the rise in ELBP (a to b) in phase with the EP rise also corresponding with a fall in venous flow. Note also the sharp increase in venous flow across the diaphragm during the relaxation phase of the maneuver (from Burns et al., 1986, with permission).

Rushmer (1947) noted that blood pressures fell more dramatically when Valsalva maneuvers were performed at high lung volumes than at the lower volume of the M-1 maneuver. It now seems that the heart–lung interactions that are seen at near-total lung capacity (such as increased right ventricular afterload at high transpulmonary pressure) may account for some of this difference.

The blood pressure fall is arrested by the onset of tachycardia and increased sympathetic arteriolar constriction. At high $+G_z$ there is preexisting tachycardia and sympathetic outflow before the M-1 maneuver is started, and muscular straining also causes sympathetic activation. Phase II falls are modest during M-1 maneuvers (Shubrooks and Leverett, 1973). However, the important feature of the M-1 maneuver is that it is "brief and repetitive" (Lambert and Wood, 1946) and, thus, the (modest) falls seen in longer strains (Fig. 5) are avoided (see Fig. 4).

Phase III

The sudden drop in arterial pressure as mouth and, hence, pleural pressure drops is due to both a direct hydrostatic effect and a sudden increase in left ventricular afterload.

Inferior vena cava flow (see Fig. 4) can be seen to be increased during phase III, presumably because the abdominal venous pressure has risen during phases I and II as a result of "damming," abdominal muscle tone and venoconstriction (Burns et al., 1986).

Phase IV

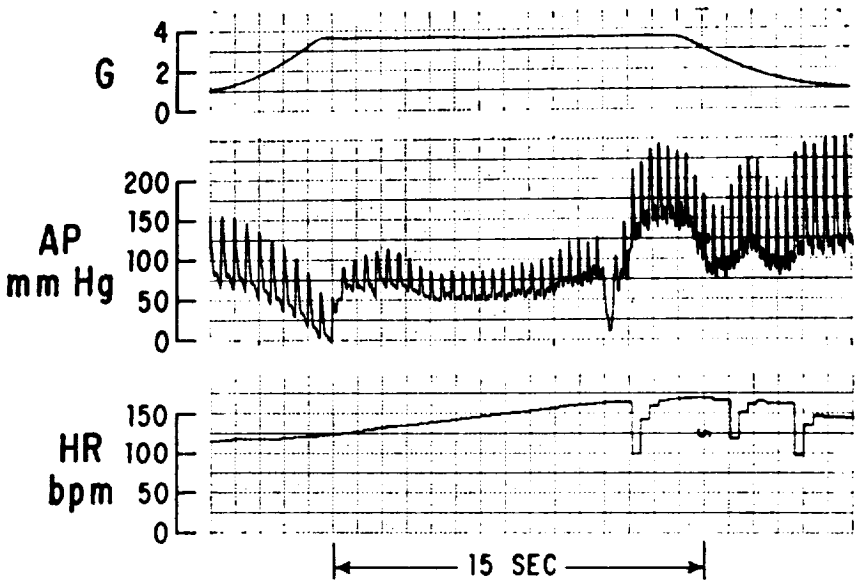
Phase IV is the overshoot phase. This is thought to be due to restoration of cardiac output into a constricted vascular bed.

In the M-1 maneuver performed at $+G_z$, the bradycardia should not be pronounced, because the carotid level pressure rise is only toward normal. Repetitive M-1 maneuvers obscure this phase, but they are, no doubt, potentiated in their pressor effect by the underlying vasoconstriction.

In summary, it is known that the M-1 and similar straining maneuvers consistently elevate blood pressure during $+G_z$. Straining enhances vasoconstriction and elevates the mean systemic pressure. The usual parasympathetic depressor reflexes are not prominent because the carotid level arterial pressure is low. The adverse effects of raised intrathoracic pressure (a fall in cardiac output and arterial pressure) can be minimized by using rapid repetitive M-1 maneuvers, where venous return and arterial pressure elevation occur in opposite phases (see Fig. 4).

G-Suit Effects

Early physiologists recognized that equal and opposite hydrostatic counterpressure would prevent the redistribution of blood during $+G_z$. Franks in



B. VALSALVA 3.7 G

Figure 5 Arterial pressure referenced to eye-level and heart rate response in humans to the Valsalva maneuver at $+3.7G_z$ without the use of a G-suit. Note the small secondary fall in blood pressure after the initial rise. The end of the maneuver is clearly indicated by the phase III fall in arterial pressure (from Shubrooks and Leverett, 1973, with permission).

1940, developed a water-filled suit of inelastic material, which extended tolerance by approximately $+1.7G_z$ (Leverett et al., 1961). Later, Webb and Gray (1960) established that total immersion made $+9G_z$ comfortable (and up to $+31G_z$ tolerable) provided breathing pressure was appropriate.

It was soon apparent that pneumatic counterpressure was more practical than immersion and that it was not necessary to simulate the hydrostatic gradient. The standard U.S. Air Force anti-G suit (USAF CSU-12/P) is representative of the current technology, which dates back to the late 1940s (Wood, 1987). Five interconnecting bladders, over the calves, thighs, and abdomen, are incorporated in a snugly fitted, adjustable, cut-away garment that is worn over the flying suit. An automatic valve admits air through the abdominal bladder. As $+2G_z$ is well tolerated, and the filling and emptying of the suit during normal turbulence and maneuvering is rather distracting, the valve is generally set to operate only at more than

$+2G_z$. A typical protocol is linear pressurization at 76 torr/G_z (1.5 psi/G_z). Whereas $+G_z$ protection on the centrifuge bears a linear relationship to applied suit pressure, extreme discomfort precludes the practical use more than 414 torr (8 psi) (Hrebien and Hendler, 1985).

The mechanism of blood pressure elevation by G-suits is controversial. The contenders are an increase in systemic venous return and an increase in total systemic resistance (TSR). The controversy may well be due to the predominance of one or the other mechanism under different conditions.

Gaffney et al. (1981) pointed out that hypovolemic subjects who benefit from medical antishock trousers (MAST) do not have a large splanchnic and lower-limb venous volume for central translocation. They found that MAST increased TSR 48% and cardiac output only 18% in their supine normal subjects.

Seaworth et al. (1985) used echocardiography to establish that G-suit inflation in the upright posture significantly increases end-diastolic volume and cardiac output and actually produces a fall in TSR.

Inflation of G-suits at $+1G_z$ does not necessarily provide good evidence of mechanisms at $+G_z$. Animal studies of inflation during $+G_z$ stress occur in the setting of established vasoconstriction. Lightly anesthetized dogs were centrifuged by Peterson and coworkers (1977) and developed very high TSRs (124% above control) at $+3G_z$. G-suit inflation to 76 torr partially restored the cardiac output, relieved the hypotension, and caused a net fall in TSR (to 60% above control). Thus, G-suit inflation must have improved the venous return.

It is dangerous to apply animal data to humans uncritically. Pigs and dogs have relatively much less blood volume in their hind limbs, and abdominal counterpressure is likely to play a greater part in the G-suit effect, especially if anesthesia is used. Conscious, permanently instrumented miniature swine are presently the best animal model, especially because they grunt and strain during $+G_z$ in a very human fashion.

Miniature swine were used in the recent study of Burns et al. (1986). Hemodynamic data from that study suggests that both an increase in TSR and improved venous return are important G-suit mechanisms. The study also documented two other important effects. The G-suit increases the efficacy of the M-1-like straining by providing a "platform" against which respiratory muscles can strain. Elevation of abdominal pressure also prevents descent of the heart. Glaister (1970) has previously described this effect in humans in whom a 2-cm descent at $+4G_z$ (causing a 6-torr eye-level blood pressure fall) can be prevented by G-suit inflation.

Pressure Breathing

It will be shown in the next section that pressure breathing elevates arterial blood pressure. Pressure breathing is associated with expiratory straining and is as effective as the M-1 maneuver in providing $+G_z$ protection, particularly when used with a G-suit. The mechanics involved are similar to those seen in the M-1 maneuver and are discussed by Shubrooks (1973).

Altering the G Axis

Acceleration is tolerated much better lying down (G_x). Aircraft seats have been developed that elevate the pelvis and legs during $+G_z$ acceleration, but this does little to address the critical problem: the hydrostatic pressure difference between head and heart.

Eventually, the wisdom of adopting the prone or supine position in fighter aircraft may become inescapable, and the interesting problem of high sustained $+G_z$ will become rather academic. This is now anything but true with rapidly escalating aircraft performance, an unchanging system of $+G_z$ orientation (dating back to the 1900s), and with protective systems largely unchanged since the 1940s (Wood, 1987).

IV. Pressure Breathing

A. Altitude Tolerance

The highest safe altitude when breathing pure oxygen at ambient pressure is about 40,000 ft (barometric pressure 141 torr, P_{AO_2} 54 torr with a P_{ACO_2} of 40 torr).

This limit was extended during World War II by using pressure breathing (PB) to maintain a higher-than-atmospheric pressure in the lungs (Barach et al., 1947). An airway pressure of 141 torr at 45,000 ft requires mask pressure of 30 torr, which is the practical limit of sustained human tolerance (Ernsting, 1966). A record 1961 glider flight to 46,266 ft still stands for that reason.

Pressure breathing, as a means of extending altitude tolerance, is now generally used only in depressurization emergencies. Modern aircraft can descend to below 40,000 ft extremely rapidly, and PB is required for only 2 or 3 minutes, at the most. Higher airway pressures (or some hypoxia) can be tolerated for such short periods, and simple mask PB systems suffice to 50,000 ft (Table 1).

United States military aviators use pressure suits when there is a risk of exposure to higher than 50,000 ft. The British, however, extend tolerance to PB using a stepwise application of counterpressure, tailored to the aircraft role. Their approach is summarized in Table 1 and is noteworthy

Table 1 Altitude Limits during Pressure Breathing

System	Mask	Mask, jerkin	Mask, jerkin, G-suit	Helmet, jerkin, G-suit	Helmet, jerkin, G-suit, arm extensions
Mouth pressure (torr)	30	50	60	107	140
Maximum altitude (1000 ft)	45	50	56	70	100
Maximum altitude (torr)	111	87	65	34	7.5

Source: after Ernsting, 1966

for its use of trunk counterpressure. Ernsting (1966) documents the extensive investigation that led to this system.

The Royal Air Force (RAF) pressure jerkin is a development of a wartime Canadian pressure vest in which mask pressure was applied to bladders in a tight-fitting waistcoat. Pressure vests of this type were extensively investigated in the United States in the 1940s, and it was recognized that an abdominal extension was required to prevent excessive descent of the diaphragm at high breathing pressures. Drury et al. (1947) found that this combined counterpressure allowed airway pressures of 45 torr to be tolerated for 10 to 20 min. The addition of a G-suit allowed subjects to tolerate 60 torr for as long as 30 min (Ernsting, 1966).

At high levels of PB, a pressure helmet is required to prevent extreme distension of the upper respiratory tract and severe pain that can cause sudden collapse. Arm pain from venous engorgement can be similarly incapacitating above 70,000 ft; therefore, arm counterpressure is required (see Table 1). Once this point is reached, the system is roughly equivalent to a "partial-pressure suit" with counterpressure over the entire body, at which point the cardiorespiratory stress of PB has largely disappeared.

B. Effects of Pressure Breathing on Lung Volume

An airway pressure of 20 torr (approx. 27 cmH_2O) will almost fully inflate the lungs of a relaxed subject. However, subjects maintain expiratory effort in response to the increased pressure. Despite this, tidal volume increases slightly, and expiratory reserve volume (ERV) increases markedly with increasing positive mask pressure, until at 30 torr (41 cmH_2O) the ERV has increased to over 80% of total lung capacity (TLC), and the inspiratory reserve volume is virtually zero. Pressure breathing at 30 torr can be tolerated for about 10 to 20 min, beyond which exhalation becomes exhausting and collapse can occur (Ernsting, 1966).

Trunk counterpressure is dramatically effective in preventing lung overdistension and easing the work of breathing. The RAF jerkin allows

only minimal increases in lung volume, which are largely attributable to a reduction in thoracic blood volume (Ernsting, 1966).

C. Cardiovascular Effects of Pressure Breathing

Findings from clinical and animal investigations of the effects of positive end-expiratory pressure (PEEP) should be applied with considerable caution in the aviation setting. Aviators resist lung overinflation and have learned to tense muscles strongly under the stresses of PB and $+G_z$. Direct investigations, however historic, should be studied first.

Peripheral Venous Engorgement

The thrust of many early investigations was to document the displacement of blood to the periphery. It was found that it took about 20 sec from the onset of PB for the peripheral venous pressure to plateau at a level approximately equivalent to the pleural pressure. Limb volume increased as venous pressure increased at about 0.018 ml·100 ml·torr) (Ernsting, 1966). Ernsting calculated that the immediate shift away from the trunk was 190 ml at a breathing pressure of 30 torr, which was consistent with the 300 ml shift that Henry (1951) had estimated at 40 torr. Ernsting's plethysmographic studies showed that there was a continuing slow increase in limb volume, doubling the fluid shift in 5 min.

This redistribution of blood is small in comparison with that seen in supine studies. Fenn et al. (1947) showed that PB at 20 torr displaced 500 ml of blood in supine subjects on a teeter board. This difference is analogous to the much larger shift of blood that occurs on going from the supine to erect position, than on going from $+1G_z$ to $+2G_z$. It probably represents the difference between filling an unstressed venous reservoir and distending an elastic one. Furthermore, pressure breathing causes active venoconstriction. Ernsting found that plethysmographic increases in limb volume were consistently less than those occasioned by equal local rises in venous pressure and that this difference was abolished by nerve blocks. Thus, there is a similarity to the Valsalva maneuver. The high tolerance of PB by aviators probably is due to venoconstriction and abdominal straining, as well as to vigorous use of the expiratory muscles.

Right Transatrial Pressure

Direct measurements of right transatrial pressures during aviators PB without chest counterpressure have not been made. However, an interesting pattern emerges when data from other sources is considered. Scharf et al. (1977) studied right transatrial pressure in dogs during PEEP, comparing a group with high lung volumes with a group with controlled

lung volumes (by use of pneumothoraces). The first group showed a rise, the second a fall in right transatrial pressure.

Cassidy et al. (1979), observed substantial increases in right transatrial pressure in normal subjects during relatively modest PEEP (7.5 torr). The subjects had been trained to relax, allowing their lung volumes to increase. Ernsting (1966) observed a fall in right transatrial pressure during PB in subjects wearing pressure jerkins. Earlier, Cournand et al. (1948) had observed a fall in right transatrial pressure during simple pressure breathing. They had, however, selected *patients with pneumothoraces* to enable accurate pleural pressure measurements. In retrospect, one can see that their anomalous results fit nicely into the pattern: PB causes a rise in right transatrial pressure if lung volume increases sufficiently.

It is not clear that aviators' PB at 7.5 torr would produce an increase in right transatrial pressure similar to that seen by Cassidy et al. (1979). At that pressure, aviators largely resist increases in lung volume (Ernsting, 1966). It seems likely that at the higher pressures used in aviation, right transatrial pressure would rise, especially toward the limit of tolerance, as lung volumes increase. Heart-lung interactions could be prominent under these conditions. Lung volumes may be sufficient to affect apparent ventricular performance (Culver et al., 1981), right ventricular afterload (Whittenberger et al., 1960), or trigger reflex cardiovascular depression (Cassidy, 1984; Ashton and Cassidy, 1985).

Effect on Arterial Blood Pressure

Aviation workers are especially interested in the acute transient blood pressure responses to the sudden onset of PB, as during both acceleration stress and rapid decompression, these transient responses might lead to sudden incapacitation. Ernsting (1966) reviewed these transient changes, which are similar to those seen with the Valsalva maneuver. There is an initial increase in arterial pressure paralleling the increase in pleural pressure, which is maintained for several seconds, followed by a fall in both mean and pulse pressure, and then a second rise, with the pressure stabilizing at a new raised value. Ernsting related this second rise to a partial restoration of venous return after filling of the venous capacitance. The prominence of rising mean systemic pressure must depend on venoconstriction, straining, and the presence or absence of a G-suit.

Ernsting (1966) explored the relationship between PB pressure and blood pressure in subjects wearing helmets. Pressure breathing caused the arterial pressure to rise by approximately 50% of the airway pressure with no counterpressure, 70% with chest counterpressure, 90% with trunk counterpressure, and 110% with trunk and lower-limb counterpressure. These results must be interpreted with caution when applied to mask PB.

Ernsting noted that the helmet bladders applied airway pressure over the carotid arteries and that deflation of the appropriate bladders caused the arterial pressure to fall by about 50% of the previously applied counterpressure. This suggests that mask PB should have less effect on arterial pressure.

Cassidy et al. (1979) reported average systolic and diastolic increases of approximately 5 torr during 1 hr of 7.5-torr PEEP. Because PB can increase arterial blood pressure, it is not surprising that it is now being investigated as a means of protection against $+G_z$. Shubrooks (1973) showed that 20 to 40 torr mask PB increased arterial pressure by approximately 25 torr at approximately $+3.5G_z$. As any carotid reflex that might limit the increase in blood pressure at $+1G_z$ would be minimized at $+G_z$ by the hydrostatic effect, one would expect mask PB pressor responses at $+G_z$ to be similar to the helmet PB response seen by Ernsting (1966), on the ground.

Effect on Left Ventricular Afterload

Left ventricular afterload is determined by the left ventricular transmural pressure (Permutt, 1973). This pressure is reduced in anesthetized dogs receiving PEEP (Scharf et al., 1980) where the rise in blood pressure is minimal and should be reduced as long as the rise in blood pressure is less than the rise in pleural pressure. Ernsting's data suggests that this holds true in aviators' PB unless total counterpressure is applied.

Pressure-Breathing Syncope

Ernsting (1966) noted that syncope usually supervened at the limit of tolerance of pressure breathing (Fig. 6). He described a biphasic fall in blood pressure. First there was a slow fall associated with an increasing tachycardia, facial pallor, and sweating. Then there was an abrupt fall in blood pressure, with bradycardia, and syncope. Ernsting noted a marked decrease in peripheral resistance of the forearm at that time. He suggested that the very small left ventricular end-systolic volume would stimulate intracardiac receptors, thus, causing reflex peripheral vasodilation and bradycardia (Sharpey-Schafer et al., 1958).

The major effect of pressure breathing on left ventricular afterload must lead to very low ventricular volumes in the face of falling arterial pressure. The mechanism described by Ernsting (1966) very closely resembles the mechanism suggested by Epstein et al. (1968) for vasovagal syncope, that was based on observations during head-up tilt and lower-body negative pressure (LBNP).

Ernsting's observations were made on subjects in pressure jerkins. In this situation, the syncope is obviously analogous to "vasovagal" fainting

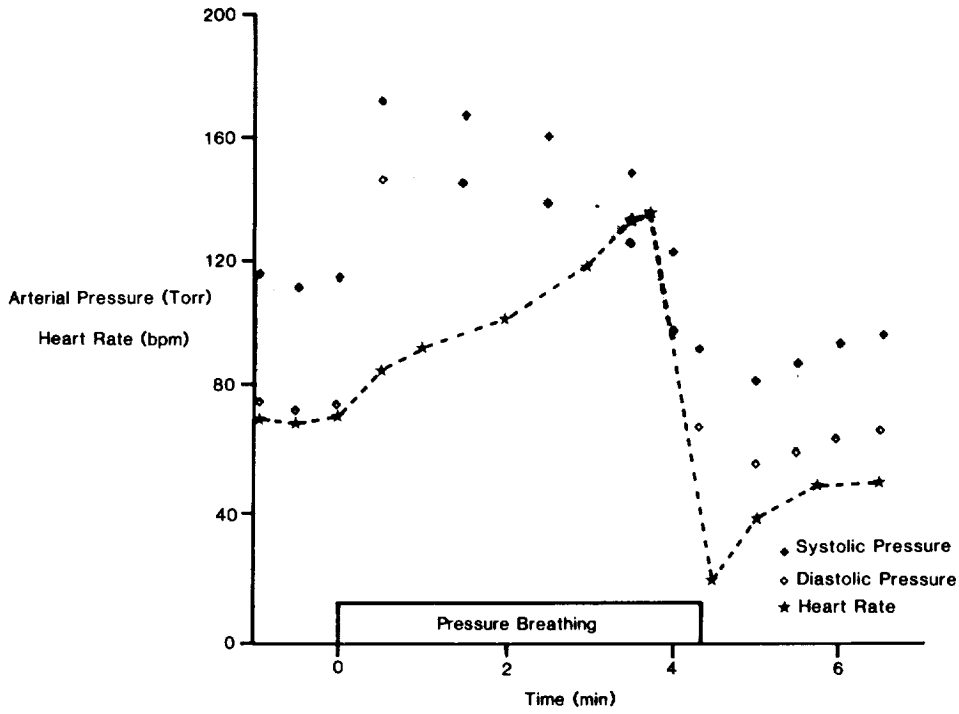


Figure 6 Pressure-breathing syncope: heart rate and blood pressure response to 80 torr of pressure breathing with chest counterpressure. Note the biphasic fall in blood pressure and the reversal of tachycardia in the second phase (from Ernsting, 1966; the original was first published in AGARD AG 106, dated 1966, by the Advisory Group for Aerospace Research and Development, North Atlantic Treaty Organization, AGARD/NATO).

seen in other settings. The syncope seen with simple mask PB may also be analogous, but other heart-lung interactions might play a larger role because respiratory muscle exhaustion could lead to extreme lung hyperinflation.

Effect on Cardiac Output

It is instructive to compare the reported effects of PB on cardiac output in different experimental settings (Table 2).

It can be seen that cardiac outputs are still 50% of normal in anesthetized dogs at 15 torr (20 cmH_2O) PB. This is possible only if the normal venous return curve shifts to the right, presumably because of

Table 2 Effect of Pressure Breathing on Cardiac Output

Experimental conditions	Change in cardiac output
Closed-chest dogs (Scharf et al., 1977)	50% fall at 15-torr PB
Relaxed humans (Cassidy et al., 1979)	20% fall at 7.5-torr PB
Aviators (Ernsting, 1965)	40% fall at 30-torr PB
Aviators, trunk counterpressure (Ernsting, 1965)	30% fall at 30-torr PB

sympathetic venoconstriction, and because descent of the diaphragm raises the abdominal pressure, shifting blood away from the splanchnic reservoir (Scharf et al., 1977). The relaxed human response to PB can be seen to be similar. Aviators' PB (nonrelaxed), can be seen to cause much less reduction in cardiac output. Straining is known to enhance venoconstriction (Browse and Hardwick, 1969), and aviators strain and maintain higher abdominal than pleural pressures to avoid lung expansion. Increased abdominal pressure increases cardiac output during PEEP (Scharf and Ingram, 1977), probably because of mobilization of blood in the splanchnic reservoir. The right shift of the venous return curve under these conditions must be large. Trunk counterpressure can be seen to lessen the decrease in cardiac output, as is consistent with current understanding of the influence of lung inflation on the right-side heart hemodynamics and with the added effect that abdominal counterpressure must have on mean systemic pressure.

D. Neurohormonal Effects

Modern aviation application of PB is of very short duration, but PB was used for prolonged periods in the 1940s and urine output fell (Drury et al., 1947). Further investigation showed that negative-pressure breathing had the opposite effect (Gauer et al., 1954; Sieker et al., 1954). This work led directly to the recognition that volume receptors must exist in the atria and pulmonary venous system (Gauer and Henry, 1963; Meehan, 1986). This topic is of great interest to investigators of the effects of microgravity and will be discussed in the next section.

V. Spaceflight (Microgravity)

Dietlein (1977) summarized the findings of the Skylab investigation of the human response to prolonged weightlessness. There was:

1. A marked shift of fluid from the lower to the upper half of the body
2. An increasing sensitivity to lower-body negative pressure during the flight
3. A small loss of circulating blood volume
4. A maintained exercise capacity in space
5. Postflight orthostatic intolerance, decreased exercise capacity while upright, and decreased cardiac size with normal contractility

It was concluded that circulatory and renal responses to an increase in central blood volume, caused by the headward fluid shift in microgravity (O-G), must play a large part in the "cardiovascular deconditioning" seen on return to $+G_z$. Parallels have been drawn to the changes seen during exposure to bed rest, supine head-down tilt, and immersion in water.

Unfortunately, many of the early hemodynamic and renal responses that are seen in these ground-based models have not been observed in microgravity. This may be because they are short-lived. Most of the cardiovascular effects seen at the onset of head-down tilt were undetectable after 6 hr (Nixon et al., 1979). Measurements were scanty in the first few days during the Skylab program, and very little relevant data has been collected since. There are other difficulties. Crews are supine and, thus, adapting to a lessened gravitational load for at least 2 hr before launch. The nausea, anorexia, and vomiting of "space sickness" can have devastating effects on any study of circulatory, neuroendocrine, or renal function during the first 2 to 3 days of flight.

In this section, we focus on the acute changes seen during the first week of weightlessness, and immediately after return to $+1G_z$. Current understanding still depends on ground-based simulations (immersion, bed rest, and head-down tilt). Blomqvist and Stone (1985), Sandler (1980), Levy and Talbot (1983a), and Greenleaf (1984) have reviewed these topics more extensively.

In this volume concerning heart-lung interactions, it is noteworthy that many of the proposed acute circulatory effects of weightlessness involve small increases in *transmural* pressures in the thoracic cardiovascular structures. It is appropriate to consider the effects of weightlessness on the lung before discussing cardiovascular changes because if weightlessness, or its simulations, causes changes in lung volumes and pleural pressure topography (as seems likely), then measured vascular pressures should be

related to the new measured, or at least calculated, pleural pressures. It will become apparent that few of the studies that follow have adequately addressed this problem: small changes in CVP, for instance, are extremely difficult to interpret without knowledge of the concomitant changes in resting lung volumes and pleural pressure, as the subject goes from $+G_z$ to O-G, or becomes immersed, recumbent, or is tilted head down.

A. Acute Effects of Microgravity

Regional Effects on Lung Function

The large topographic gradients in alveolar size, ventilation, and pulmonary blood flow that are seen at $+1G_z$ (Glazier et al., 1967; West et al., 1964) should virtually disappear in microgravity (Glaister, 1977). Virtual weightlessness can be sustained for 20 to 40 sec in aircraft, enabling studies of the effect of short-term microgravity on lung function.

Ventilation

Michels and West (1978) performed combined single-breath nitrogen-argon bolus washout tests during LearJet parabolas. The cardiogenic oscillations of both resident and bolus inert gases virtually disappeared; thus, topographic gradients in alveolar size and ventilation had decreased markedly (Fig. 7).

There were small terminal nitrogen rises (phase IV) on many of the LearJet O-G tracings suggesting the presence of minor nongravitational inhomogeneity of airways closure, as predicted by Glaister (1977). It is possible that vascular engorgement is, at least partly, responsible for this effect. Head-out immersion in water causes a cephalad blood redistribution and an increase in closing volume. It has been shown that much of this increase can be prevented by cuffing the limbs, thereby decreasing central vascular engorgement (Bondi et al., 1976).

The suggestion has been made that the diaphragm should adopt a more cephalad position at O-G and, thus, FRC may be reduced. An increase in thoracic blood volume may possibly account for the 10% reduction in vital capacity that was seen in Skylab-4 crews in orbit (Levy and Talbot, 1983b).

It seems highly unlikely that gas exchange will be compromised because of any of these effects. Rather, it seems that ventilation should become strikingly more uniform in the microgravity environment. Furthermore, because vascular engorgement should decrease with adaptation, any terminal airways closure and vital capacity reduction may also decrease.

Perfusion

Stone et al. (1965) injected ^{131}I-labeled, macroaggregated albumin intravenously during parabolic flight and scanned immediately postflight.

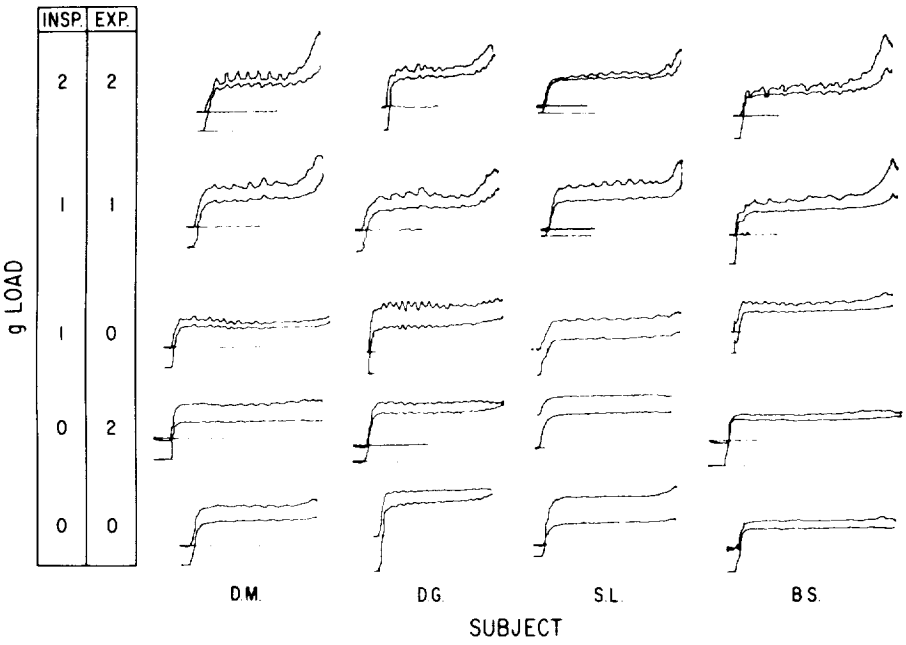


Figure 7 Comparison of single-breath washouts from four subjects (columns) at various gravitational loads (rows) with inspiratory and expiratory G_z levels indicated on the left. For each, the upper curves are Ar-bolus washouts, and the lower are N_2 washouts. Expired volume is plotted along the abscissa and normalized gas concentrations are plotted along the ordinate.

Notice the virtual absence of cardiogenic oscillations in phase III when inspiration is carried out at O-G and the strong dependence of the magnitude of the cardiogenic oscillations on inspired G_z level. Note the near disappearance of phase IV in some subjects at O-G (from Michels and West, 1978, with permission).

They found a considerable shift in blood flow toward the lung apices. Michels and West (1978) showed that cardiogenic oscillations of oxygen and carbon dioxide virtually disappeared at O-G, suggesting that the topographic gradient in gas exchange had markedly lessened. Both studies are consisstent with the topographic perfusion model (West et al. 1964; see Sect. III.B) that relates blood flow to arterial and venous hydrostatic gradients in the presence of a uniform alveolar pressure. This model predicts uniform blood flow at O-G.

Capillary Distension

The apical regions of the lung will be subject to greater capillary recruitment at O-G, and the thoracic blood volume should be increased. Furthermore,

there is increasing evidence that left ventricular preload (and, thus, pulmonary venous pressure) increases at the onset of head-down tilt and O-G (see under Sect. V.B). Nixon et al. (1979) showed not only an increased left ventricular preload during the first 24 hr of 5-degree head-down tilt but also that the DLCO increased significantly, suggesting an increase in pulmonary capillary blood volume. In fact, there may well be more filling of the pulmonary capillaries for a given set of pulmonary arterial and pulmonary venous pressures in the absence of gravity. A small increase in pressure should equally affect all pulmonary capillaries in the absence of hydrostatic gradients.

Gas Exchange

The LearJet data of Michels and West (1978) suggest that topographic gradients in ventilation perfusion ratio ($\dot{V}_A/\dot{Q}_c$) should virtually disappear. However, it is possible that intraregional gas exchange may become compromised by increases in capillary pressure and transudation, especially under conditions of exercise. This possibility has been proposed for many years (Permutt, 1967), but it has not yet been tested. Cohen et al. (1971) noted a widening in A-a oxygen gradients during head-out immersion but, there, the major mechanism is almost certainly the low lung volume in the presence of increased dependent airways closure (Bondi et al., 1976).

Pleural Pressure

Pleural pressure rises considerably during head-out immersion: Arborelius et al. (1972) observed a rise of 5 ± 2 mmHg (7 ± 3 cmH_2O). This is associated with a fall in FRC of over 1 L (Bondi et al., 1976).

Agostoni (1985) estimates, on the basis of an extensive review, that at FRC, pleural pressure is about − 6 mmHg (− 8 cmH_2O) just below the lung apex, and − 1.5 mmHg (− 2 cmH_2O) at the lung base when sitting erect, and − 3 mmHg (− 4 cmH_2O) at the lung apex and 0 mmHg (0 cmH_2O) at the base in the supine posture. It is noteworthy that he considers that pleural pressure at the resting volume of the respiratory system is more subatmospheric at apex than at base in all postures. In space, if this still holds true, and if resting lung volumes are decreased, as they are in recumbency, basal pleural and, by inference, pericardial pressure may be increased. One hopes that this speculation about pleural pressure change at O-G is tested before too much is made of small measured changes in CVP or atrial pressure and that future CVP measurements in space (and during tilt simulation) are related, at least, to any changes in FRC or esophageal pressure.

Circulatory Changes

Volume Redistribution

Simulations suggest that the cephalad fluid shift occurs in two phases: First, a shift of blood should occur and be complete within 20 to 30 sec (Sjöstrand, 1953). Arborelius et al. (1972) measured an abrupt increase in thoracic blood volume of 700 ml during head-out immersion. The erect–supine transition leads to a similar shift (Blomqvist and Stone, 1985). Second, there is a shift of extracellular fluid that can lead to a transient phase of plasma expansion. McCally et al. (1966) measured a 4.3% decrease in hematocrit 25 min after initiating immersion, which suggested a 9% increase in plasma volume. Hagen et al. (1978) saw a 440-ml expansion of plasma volume after 35 min in the supine posture.

The sum of the shifts observed in both immersion and bed rest can be seen to lie in the 1 to 2 L range.

Right Atrial Pressure: Right Ventricular Preload

Head-out immersion leads to a central venous pressure (CVP) increase, of about 12 torr above supine control values, that persists almost unchanged for 3 hr (Echt et al., 1974). On the other hand, head-down tilt studies showed smaller increases in CVP from supine control readings and Nixon et al. (1979) found that CVP was back to the supine baseline within 90 min of the onset of a 5° head-down tilt. Gaffney et al. (1985) showed a more prolonged CVP rise in a very similar study on older subjects. Katkov et al. (1979) saw no increase in right atrial pressure during a 15° head-down tilt study. Gauer and Thron (1965) found that the hydostatic indifference point, normally just below the diaphragm, moves to a point just above the atria during head-down tilting. The fact that the right atrium is so close to this point makes the modest and variable effect of tilt understandable. These big differences between immersion and tilt studies pose the question: Is either model appropriate?

A prolonged CVP rise was seen in an orbiting macaque monkey (Meehan, 1971), and Soviet investigators have reported sustained jugular venous pressure increases (Levy and Talbot, 1983a). However, Kirsch et al. (1984), who estimated CVP in Spacelab-1 crewmembers from antecubital vein measurements, concluded that it had fallen. Unfortunately, the first inflight measurement opportunity was after 20 hr in orbit. Direct early measurements of CVP are planned during the Spacelab Life Sciences-1 (SLS-1) mission (West, 1984), and there is a wide consensus that further ground-based modeling is of very little value without this information (Levy and Talbot, 1983a, 1983b).

Pulmonary Arterial Pressure: Right Ventricular Afterload

Arborelius et al. (1972) mesured pleural, pulmonary arterial (P_a), and right atrial pressure during head-out immersion. The pleural pressure rose 5 mmHg (FRC is reduced markedly during immersion), and the mean transmural P_a and right atrial pressures increased by about 13 torr.

Katkov et al. (1983) measured vascular pressures, but not pleural pressure, during a 7-day, 15° head-down tilt study. The mean P_a pressure rose slightly from 13.6 to 16.8 torr for the first 7 hr after transition from the supine control state. It is possible, however, that there was no transmural pressure rise: head-down tilting may reduce lung volumes, and thus, increase pleural pressure, and pleural pressure topography must also change.

It is widely recognized, however, that the absence of hydrostatic pressure gradients within the thorax at O-G may profoundly affect hemodynamics. Pulmonary vascular resistance should be lower for any given flow if the recruitment and distension of the capillary bed is topographically homogeneous. It is interesting that echocardiography, after 4 hr in orbit, showed decreased right ventricular end-systolic dimensions (Bungo et al., 1986 and personal communication).

Pulmonary Venous Pressure: Left Ventricular Preload

Left ventricular end-diastolic diameter seems to increase during the first 24 hr of head-down tilt, with an associated increase in stroke volume but a decrease in heart rate (Nixon et al., 1979). Pottier et al. (1986) have reported echocardiographic evidence for a 15% increase in left ventricular end-diastolic volume during the first 4 days of spaceflight. Recently, Bungo et al. (1986) found that while left ventricular end-diastolic volumes increased after 4 hr of microgravity, they were decreased below baseline on the second and subsequent days of flight.

Arterial Pressure: Left Ventricular Afterload

All Skylab crews had lower mean arterial pressures than those measured preflight (Johnson et al., 1977).

Cardiac Output

Head-out immersion can produce an over 30% increase of both cardiac output and stroke volume that shows no tendency to decrease after several hours (Arborelius et al., 1972; Begin et al., 1976).

Head-down tilt, in young male subjects, increased stroke volume but not cardiac output (Nixon et al., 1979). A later study of middle-aged subjects, by the same group (Gaffney et al., 1985), demonstrated an increase in both stroke volume and (for less than 4 hr) cardiac output. In other words, bradycardia was a significant mechanism in the younger but not in the older subjects. Despite the increase in cardiac output in the older subjects, arterial pressure was controlled by vasodilation. All hemodynamic

changes had returned to baseline in 20 hr in the tilt study of Gaffney et al. (1985), and they were smaller in magnitude than in the earlier immersion studies.

There is speculation that fluid shifts should lead to a rise in preload early in spaceflight, but whether or not the observation by Bungo et al. (1986) of an increased left ventricular end-diastolic volume is respresentative, and whether or not this is associated with an increase in cardiac output remains to be seen.

B. Adaptations to Microgravity

Negative Fluid Balance

Weight loss of 1 to 2 kg, approximately corresponding with the cephalad fluid shift, is seen within 3 to 4 days during bed rest and within 1 to 2 days during head-down tilt and space flight. Weight loss during water immersion is faster and can be more than 1 kg in 6 hr (Blomqvist and Stone, 1985).

Atriorenal Reflex

An atriorenal reflex (Gauer et al., 1970) that leads to an appropriate diuresis as central blood volume increases has a well-established role in the dog (Menninger, 1985). Dog low-pressure cardiac receptors are demonstrably more sensitive to small blood volume changes than are arterial baroreceptors (Gupta et al., 1966) and, through vagal afferents, tonically inhibit ADH release. Both of these low-pressure receptors and carotid sinus receptors also restrain the release of renin (Thames et al., 1978; Thames and Schmid, 1981). Cardiac denervation experiments attenuate the vasopressin response to hemorrhage (Wang et al., 1983) and grossly disrupt the relationship between osmolality, vasopressin, and blood volume (Wang et al., 1984).

Other Causes of Diuresis

In primates, there is a greater redundancy of mechanisms to defend the blood volume: cardiac denervation has either no effect on, or merely blunts the renal response to, volume loading (Peterson et al., 1983; Peterson and Jones, 1983; Cornish and Gilmore, 1982; Gilmore, 1983). Sinoaortic baroreceptors may play a more prominent role in vasopressin release (Menninger, 1985). There is also increasing awareness that atrial distension evokes other responses including an independent natriuresis which persists after vasopressin administration. Its rapid onset suggests that mechanisms other than aldosterone suppression are involved (Epstein et al., 1972), and a number of mechanisms, including the release of prostaglandin E and redistribution of renal bloodflow, have been suggested (Epstein, 1978). Atrial natriuretic factor may be involved, and this agent may also suppress renin release (Burnett et al., 1984).

Lack of Evidence for Diuresis in Spaceflight

The expected early diuresis was not observed during the Skylab program (Dietlein, 1977). Although ADH excretion levels were generally reduced during the Skylab program, there were some unexpected increases. These have been attributed to a negative fluid balance caused by such factors as decreased fluid intake and frank motion sickness (Leach and Johnson, 1985). Another increasingly recognized factor is the operationally necessary prolonged prelaunch recumbency: adaptation to this state may be well advanced at the time of transition to O-G. The O-G transition may not, therefore, represent a significant thoracic volume challenge.

Greenleaf (1985) speculates that atrial stretch occasioned by transition to O-G may be insufficient to trigger the rapid "Gauer-Henry" reflex, but may be sufficient to release natriuretic peptides and, thus, cause a slow secondary volume adjustment.

Circulatory Adaptations

Changes in Venous Compliance, Autonomic Changes

Yegorov (1979), using an occlusion plethysmographic technique, demonstrated a decrease in leg venous tone during Salyut-6-Soyuz flights. Echt et al. (1974) observed a rapid decrease in elasticity in arm veins at the onset of thermoneutral immersion, followed by a continuing decline in elasticity coefficient.

Large changes in venous tone can have very dissimilar effects on blood distribution in different gravitational orientations and states. Head-out immersion increases the pressure gradient across the diaphragm (Hong et al., 1969). Under these circumstances, a relaxation of splanchnic and peripheral venous tone must have little effect on the blood shift to the intrathoracic compartment. The same argument could be applied to supine head-down tilt; it seems intuitively obvious that in the extreme event of relaxed inversion, the major caudal capacitance vessels will remain collapsed, no matter what the state of venoconstriction. On the other hand, extravascular pressures may be sufficiently uniform during weightlessness for venous unstressed volume and capacitance changes to substantially alter the distribution of blood between the intrathoracic and other compartments, thus, decreasing any major initial increase in intrathoracic blood volume.

Cardiac Effects

It is know that the circulatory blood volume is reduced after spaceflight (Blomqvist and Stone, 1985; Johnson et al., 1977). There is recent evidence that cardiac volumes are reduced below baseline supine values within 4 days of microgravity exposure (Bungo et al., 1986). Henry et al. (1977) found a similar reduction in cardiac volumes and a small decrease in

estimated left ventricular mass in two of three subjects after prolonged spaceflight, but found no change in intrinsic cardiac performance. Soviet (Rokhlenko and Mul'Diyarov, 1981) and American (Philpott et al., 1985) investigators have both reported ultrastructural myocardial abnormalities in rats exposed to short-term microgavity.

C. Postflight Effects

Orthostatic Intolerance

Postflight faintness on standing is common. Passive standing, 70° head-up tilting (Fig. 8), and lower-body negative pressure (LBNP) have consistently led to more disturbance postflight than preflight. Pulse rates are higher,

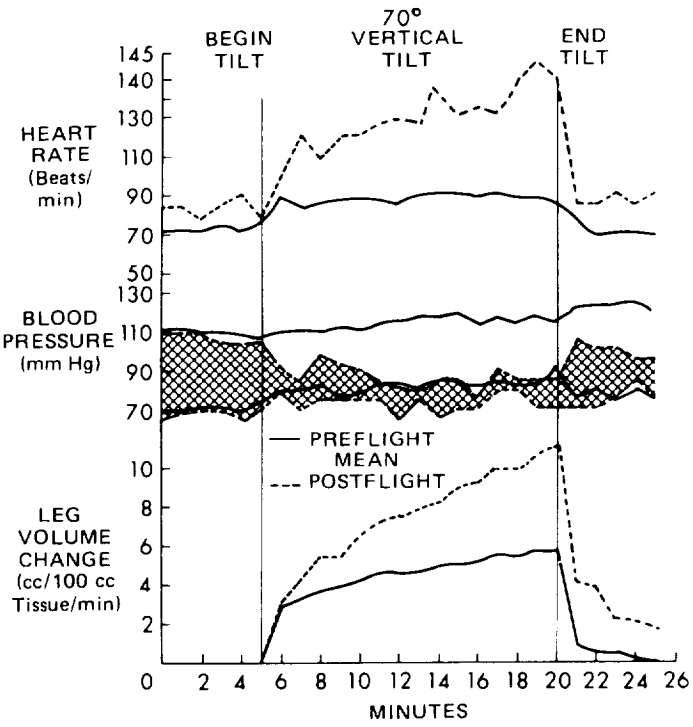


Figure 8 Tilt-table data from one subject before and after spaceflight (Gemini 7). Note the larger postflight (dashed and hatched) effects on heart rate and blood pressure and the apparent increase in leg volume change. The Whitney strain gauge measurement of leg volume change is of doubtful validity—see text (from Dietlein, 1977, with permission).

systolic blood pressures are lower, pulse pressures are narrower, and cardiac outputs are decreased (Sandler, 1980). This was initially attributed to an increase in venous pooling, as evidenced by Whitney strain gauge and capacitance band measurements of leg volume (see Fig. 8) (Johnston et al., 1977; Thornton and Hoffler, 1977), but this observation is suspect. Both of the preceding techniques detect relative volume changes, rather than absolute volume values, and are sensitive to the decrease in leg volume that occurs in flight and in simulations. Musgrave and coworkers (1969), who used a water plethysmographic technique, showed no increase in pooling after bed rest. There is a 50- to 60-ml decrease in left ventricular end-diastolic volume after 50 torr LBNP, both before and after bed rest, despite a marked increase in the other indicators of orthostasis (Sandler, 1980; Sandler et al., 1977).

After Skylab missions, left ventricular end-diastolic volume was significantly decreased (Henry et al., 1977), as was blood volume (Johnson et al., 1977). Tissue pressure falls in normally dependent regions during adaptation to head-down tilt (Hargens et al., 1983). This presumably also occurs in weightlessness and sets the stage for a further decrease in blood volume when hydrostatic gradients are restored, a result of rapid reestablishment of normal tissue volumes and pressures by transudation. Despite the ingestion of 1 L of saline before reentry, postflight echocardiograms of shuttle crew members have shown low end-diastolic volumes and stroke volumes (Bungo et al., 1987). Hypovolemia and left ventricular volume reduction set the stage for an increased sensitivity to similar amounts of pooling.

Vasovagal Fainting

Epstein and associates (1968) have described the sequence of events that occur in normal subjects on tilting or exposure to LBNP. Pooling decreases left ventricular preload and tends to lower blood pressure. If this occurs, the reduction in left ventricular afterload should lead to a gross reduction in left ventricular end-systolic volume, which may stimulate intracardiac receptors causing bradycardia, vasodilation in muscles, and collapse. After spaceflight, when left ventricular volumes are already reduced, orthostasis can readily lead to fainting.

To avoid orthostatic collapse, a brisk autonomic response is required. However, baroreceptor stimulus response curves may alter during spaceflight in the absence of normal inputs, and decreased sympathetic traffic to the peripheral vasculature may cause depletion of the endogenous catecholamine stores. Schmid et al. (1971) and Steinberg (1980) demonstrated that norepinephrine infusion after bed rest produced a normal increase in venous tone, but tyramine (which releases endogenous catecholamines) did not.

Many mechanisms may, therefore, contribute to postflight "cardiovascular deconditioning." The latter term is unfortunate if applied to the total postflight syndrome, because there are almost certainly muscular and neural adaptations to microgravity that contribute to the weakness and diminished exercise tolerance observed postflight.

Artificial Countermeasures to Adverse Effects

Reducing Inflight Adaptation

Greenleaf (1984) and Blomqvist and Stone (1985) have reviewed the countermeasures that have been proposed to improve orthostatic tolerance and point out that the flight environment is not only hypogravic, but it is also hypodynamic: little exertion or movement is required in space. Exercise of leg muscles during bed rest can decrease orthostatic intolerance, whereas continuing gravitational stress (periodic standing, chair sitting) without exercise is ineffective. More pronounced stress (LBNP, $+G_z$) can be an effective countermeasure without exercise. Exercise has become a routine countermeasure on all spaceflights, but this has not eliminated orthostatic intolerance (Greenleaf et al., 1975; Johnson et al.; 1977; Kakurin et al.; 1980; Sandler, 1980).

The Soviets use volume-redistribution devices inflight as a means of reducing adaptation. The "Chibis" vacuum suit, a variant of a lower-body negative pressure device, is used towards the end of a mission, once every 4 days for 20 min and, then, 50 min a day for the last 2 days (Gazenko et al., 1981; Nicogossian and Parker, 1982).

Decreasing Postflight Effects

Water and salt loading just before reentry has been shown to reduce the postflight orthostatic fall in blood pressure otherwise observed in shuttle crews (Bungo et al., 1985). Fluid loading (ingestion of approximately 1 L of water plus 8 g of salt tablets) before reentry is now required as a means of reducing postflight orthostatic intolerance in shuttle crews. Unfortunately, this requirement tends to confound further investigation.

G-suits are available to shuttle crews for use during reentry when up to $+2G_z$ can be experienced (a level that may have a marked effect on a deconditioned subject). Their use is, however, at the discretion of the wearer. G-suits and pressure-gradient elastic leotards have also been used postflight with considerable efficacy (Buyanov et al., 1967; McCally et al., 1968; McCally and Wunder, 1971; Miller et al., 1964).

VI. Conclusions

Aviators tolerate pressure breathing (PB) remarkably well for the short periods used operationally. This may be the reason for the very few

published reports of its effects. There has long been an appreciation that left ventricular afterload is reduced during PB, despite elevation of arterial pressure. It has been assumed that diminished venous return is entirely responsible for decrease in cardiac output. There has been little appreciation of the effects of PB on right ventricular function, probably because the best studies have been performed with trunk counterpressure limiting lung expansion. It is obviously time to reexamine this topic, in the light of the findings during modest PB in relaxed humans and animals, and especially because trunk counterpressure is not used in most aviation applications, including protection against the effects of $+G_z$.

It seems that resisted PB leads to much less reduction in cardiac output than relaxed PB. Some of this difference may be due to lowering of lung volume, but much must be due to a greater shift of the venous return curve to the right. There is obviously considerable utility in any adaptation that balances a rise in intrathoracic pressure with a rise in mean systemic pressure. Straining would seem to do this by inducing concurrent increases in abdominal muscle tone and venous tone. These mechanisms probably evolved to protect the circulation during vigorous straining with a closed glottis (for example, during heavy lifting in humans).

There are obvious parallels between the mechanisms affording protection during straining with a closed glottis, and the mechanisms that extend $+G_z$ tolerance. Pigs illustrate this on the centrifuge when they alternately strain with a closed glottis (which raises eye-level arterial pressure), then, briefly relax (which allows venous return), in an optimum repetitive sequence and, thereby, extend their $+G_z$ tolerance.

Centrifuge studies may reveal other heart–lung interactions. For example, basal pleural pressures can be elevated and the lung compressed by $+G_z$ with G-suit inflation, and there is some evidence that even elevated atrial pressures do not restore cardiac output. These observations could obviously be related, but coordinated measurements of intracardiac and extracardiac pressures have not yet been made.

There has been speculation that major heart–lung interactions should occur in microgravity. A "working hypothesis" was developed after Skylab that a headward redistribution of blood and extracellular fluid should initially expand the intrathoracic vascular compartment. This should lead to a number of adaptations including diuresis which, in turn, might lead to, or at least augment, the orthostatic intolerance seen after flight. We wish we were able to review a coordinated investigation that had tested this hypothesis. The Spacelab Life Sciences-1 Mission includes several human investigations that should go a long way toward this goal. Serial measurements will be made during the 7-day flight, and both preflight and postflight. Central venous pressures and echocardiographic

volumes will be a major part of a cardiology investigation. Estimations of pulmonary blood flow and tissue volume will be made both at rest and during exercise, and capillary volume estimations will be made at rest. A comparison of the time course of changes of these variables with changes in body mass, urine flow, and endocrine status may allow future reviewers to be less speculative.

Abbreviations and Symbols

A-a gradient:	alveolar–arterial O_2 gradient
ADH:	antidiuretic hormone
CVP:	central venous pressure
DLCO:	diffusing capacity of the lung for carbon monoxide
ERV:	expiratory reserve volume
FIO_2:	inspired fraction of O_2
FRC:	Functional residual capacity
G:	acceleration normalized to gravitational acceleration (a/g)
$+G_x$:	increased back-to-front acceleration (eyeballs-in)
$+G_y$:	increased left-to-right acceleration (eyeballs-left)
$+G_z$:	increased foot-to-head acceleration (eyeballs-down)
LBNP:	lower-body negative pressure
LVEDP:	left ventricular end diastolic pressure
MAST:	medical antishock trousers
M-1:	the M-1 anti-G straining maneuver
P_A:	alveolar pressure
$PACO_2$:	alveolar partial pressure of CO_2
PAO_2:	alveolar partial pressure of O_2
P_a:	pulmonary arterial pressure
PaO_2:	arterial partial pressure of O_2
PB:	pressure breathing
PEEP:	positive end-expiratory pressure
P_v:	pulmonary venous pressure
TLC:	total lung capacity
TSR:	total systemic resistance
$\dot{V}_A/\dot{Q}_c$:	ventilation/perfusion ratio
O-G:	weightlessness (in reality: microgravity)

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